Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: Relation to age and risk factors

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Coronary heart disease (CHD) remains the major cause of death in the United States, responsible for more than 500,000 fatalities annually. Many of these deaths are sudden and often without any prior warning signs or previously known coronary disease.[1] CHD is not normally suspected until symptoms occur or a positive stress test result is documented. The exercise treadmill test and other measures that depend on functionally significant disease are of limited use, often showing negative results in individuals who eventually have clinical coronary events.[2-5] In individuals who have no symptoms, risk is normally estimated on the basis of a family history of premature CHD and the risk factors present; however, this information alone is of limited predictive value.[6] For example, it is known that most coronary patients have only average or moderately elevated cholesterol levels.[7,8] This suggests the need for improved prediction, possibly aided by detection of preclinical coronary artery disease in individuals with no symptoms.

Pathologic studies have documented a close correspondence between coronary artery calcium (CAC) deposits and atherosclerotic plaque,[9-11] with high sensitivity for predicting advanced lesions. Among accident or other noncoronary autopsy studies recently completed in young adults, CAC deposits have also been documented, demonstrating potential value as an early marker of CHD.[12] Studies done in patients with symptoms show that those with radiographically (by fluoroscopy) detectable CAC deposits have been noted to have a higher risk of coronary events[13] or mortality[14] compared to those without CAC, but another study in patients with no symptoms showed no association with mortality.[15] Detection of CAC deposits by fluoroscopy or conventional computed tomography (CT) has been used to screen for CHD, but are of limited sensitivity.[16-19]

Ultrafast CT is the first noninvasive method to determine the arterial site and quantify the relative burden of CAC deposits as a marker of atherosclerosis. It is also sensitive for the detection of significant angiographic disease[20,21] and allows for rapid image acquisition, reduction of cardiac motion artifacts, and high-contrast resolution. CAC deposits determined by ultrafast CT have also been recently shown to be closely related to the presence and extent of extracoronary atherosclerosis in individuals with hypercholesterolemia and no symptoms.[22] The use of ultrafast CT for screening the individual with no symptoms or documented CHD, however, is controversial. Our report describes the prevalence, arterial location, and extent of CAC deposits seen in a large cohort of men and women without symptoms or documented coronary disease, including the relationship of calcium to age and coronary risk factors, and considers the implications for population screening of CHD.

METHODOLOGY

Study population and interview. Our report includes all men and women self-referred (or referred by their

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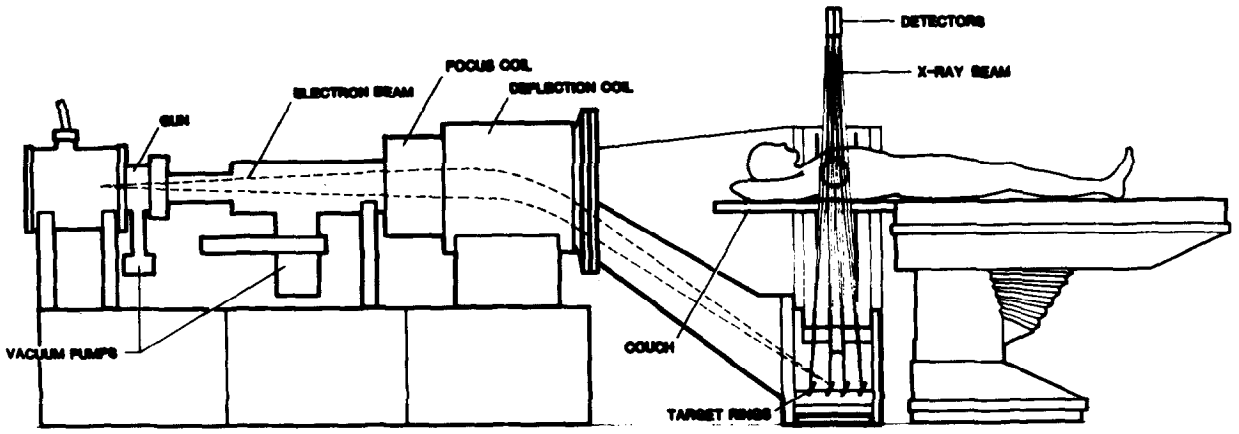

Fig. 1. Patient positioned in Imatron C-100 Ultrafast CT scanner.

physician) to a private medical clinic for ultrafast CT screening between May 1991 and December 1992, usually as a result of known coronary risk factors or a family history of CHD and risk factors. All patients received a questionnaire regarding their medical and risk factor history, history of hypertension, diabetes, hypercholesterolemia, tobacco use, current weight and height, family history of premature myocardial infarction (aged 55 or earlier in parent or sibling), chest pain suggestive of angina pectoris (by Rose questionnaire), a reported previous myocardial infarction, revascularization, or a positive angiogram. Use of medications to control hypercholesterolemia, hypertension, or diabetes were included in the category of a history of these conditions, and the number of cigarettes consumed or time since quitting was also recorded. A physician reviewed the completed responses for selected items with each subject. Subjects with a history of chest pain or previous coronary disease (myocardial infarction, bypass surgery, angioplasty, or a positive angiogram) were excluded from the current study.

Procedures for ultrafast computed tomography. All studies were performed by a standard protocol previously described[20] with an Imatron C-100 Ultrafast (Imatron, South San Francisco, Calif.) CT scanner. In brief, this protocol involved subjects being in the supine position head first into the scanning aperture with no couch angulation and instructed to take three deep breaths and hold them (at end-expiration) while a preview scan was performed. Fig. 1 shows a schematic diagram of patient positioning in the scanner. Patient positioning was checked and, if necessary, adjusted, so that scanning started from near the lower margin of the bifurcation of the main pulmonary artery. Coronary visualization was achieved without contrast by using the high-resolution volume mode of the ultrafast CT scanner in conjunction with a 100 msec scan time, 3 mm slice thickness, electrocardiographic triggering (to 80% of the R-R interval), and breath holding for approximately 45 seconds. Twenty to 30 contiguous slices were acquired with no interslice gaps. Each of the levels (which encompassed the proximal portions of the coronary arteries where nearly all calcium is present[20]) were evaluated sequentially to determine the presence and quantity of CAC deposits. From the established protocol[20] the threshold for a calcified lesion was set at a CT density of 130 Hounsfield units (HU) in at least 1 pixel (an area $\geq$ 0.51 mm^2). At each level all pixels with a CT density $\geq$ 130 HU were displayed. A region of interest was manually encircled around each visible lesion within each coronary artery, and computer-acquired measurements of lesion area in square millimeters and maximum Hounsfield number of each region of interest were recorded. A density score was determined on the basis of maximum Hounsfield number in the following manner: 1 = 130 through 199, 2 = 200 through 299, 3 = 300 through 399, and 4 = >400 H.U. Fig. 2 displays examples of encircled calcified lesions in the left anterior descending and left circumflex arteries, with assigned volume and density scores in the case of a patient with severe CAC deposits. A score for each region of interest was calculated by multiplying density score by area. A total calcium score was determined by adding up each of these scores for all 20 slices. Total scores were also obtained for each of the following major coronary arteries: (1) left main, (2) left anterior descending, (3) left circumflex, and (4) right coronary artery.

Statistical analyses. The prevalence of detectable CAC deposits (total calcium score of >0) and mean total score were calculated initially, separately for men and women with no symptoms across age groups

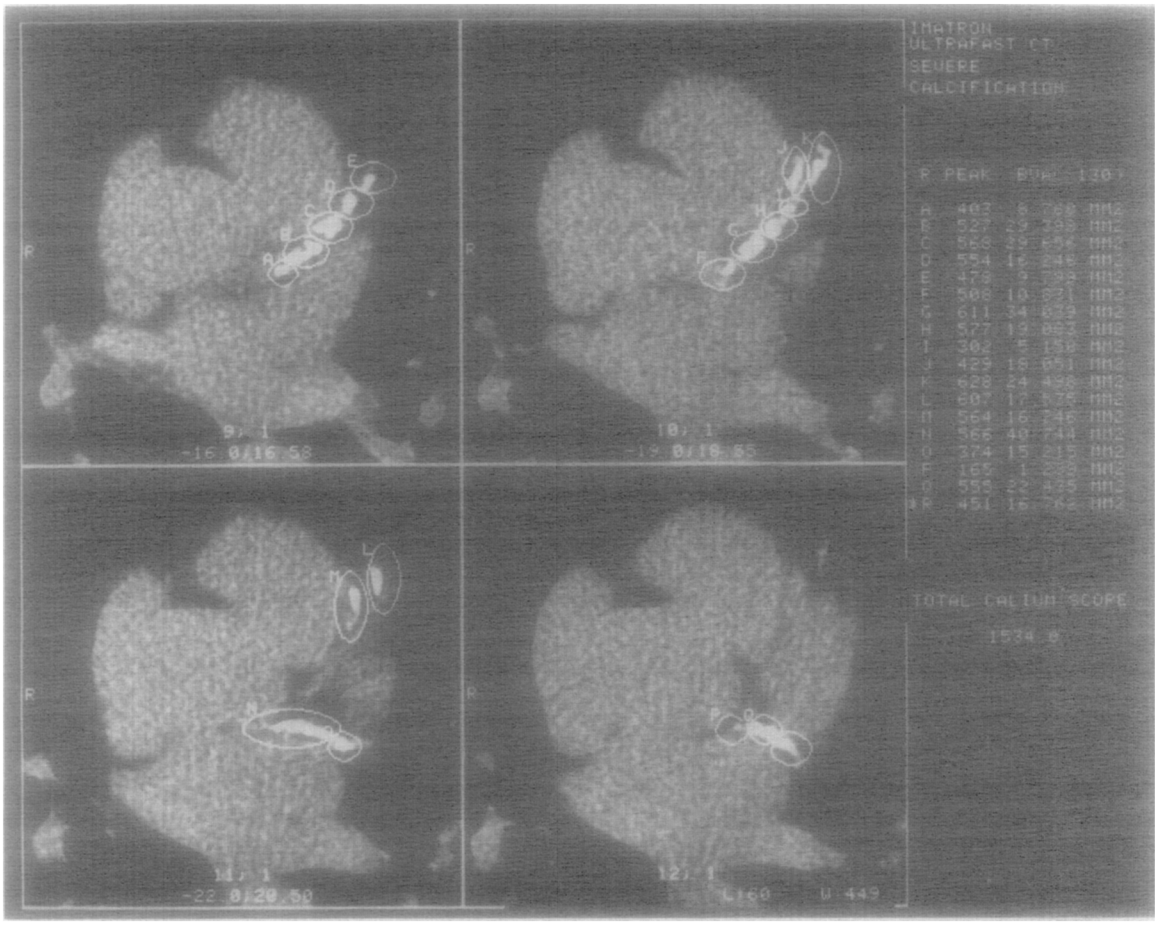

Fig. 2. *Example of selected tomographic slices in patient with severe CAC deposits (total score = 1534) showing encircled calcified lesions in left anterior descending (A-L) and left circumflex (P-R) arteries.*

(<40 years, 40 through 49 years, 50 through 59 years, 60 through 69 years, and >70 years) for all arteries and for each major coronary artery. Analysis of variance (with the natural logarithm of 1 plus the total calcium score to normalize data) and overall chi-square analyses were done separately in men and women to examine for age-related differences in calcium score and prevalence, respectively.

Separately, for men and women without symptoms, the chi-square test was used to compare the proportions of individuals with detectable calcium by reported history of (1) high blood pressure, (2) diabetes, (3) hypercholesterolemia, (4) family history of premature (before age 55 years) myocardial infarction in sibling or parent, (5) current or previous tobacco use, (6) infrequent exercise (less than once a week and of light intensity), and (7) obesity (determined as being in the upper quintile of body mass index). Risk ratios (defined as prevalence odds ratios in this cross-sectional evaluation) were also calculated. The mean natural logarithm of calcium score (after adding 1) and prevalence of detectable CAC deposits were also compared for those with 0, 1, 2, 3, or more principal risk factors (high blood pressure, diabetes, hypercholesterolemia, smoking, or family history of premature myocardial infarction) by analysis of variance or chi-square analyses as appropriate. The prevalence of CAC deposits by number of risk factors (0, 1, or 2 or more) was also examined by age group (<50, 50 through 59, and ≥60) in a similar manner.

Stepwise multiple logistic and multiple linear regression analyses were done to examine for variables that contributed significantly to predicting the presence and mean natural logarithm of CAC deposits, respectively. Complete risk factor data for these analyses were available on 800 subjects. Alpha levels of 0.10 were required for a variable to enter and remain in the model. Risk ratios (RR) and 95% confidence intervals were calculated for the odds of CAC deposits being present in those with versus without a history of each selected risk factor, gender, and age.

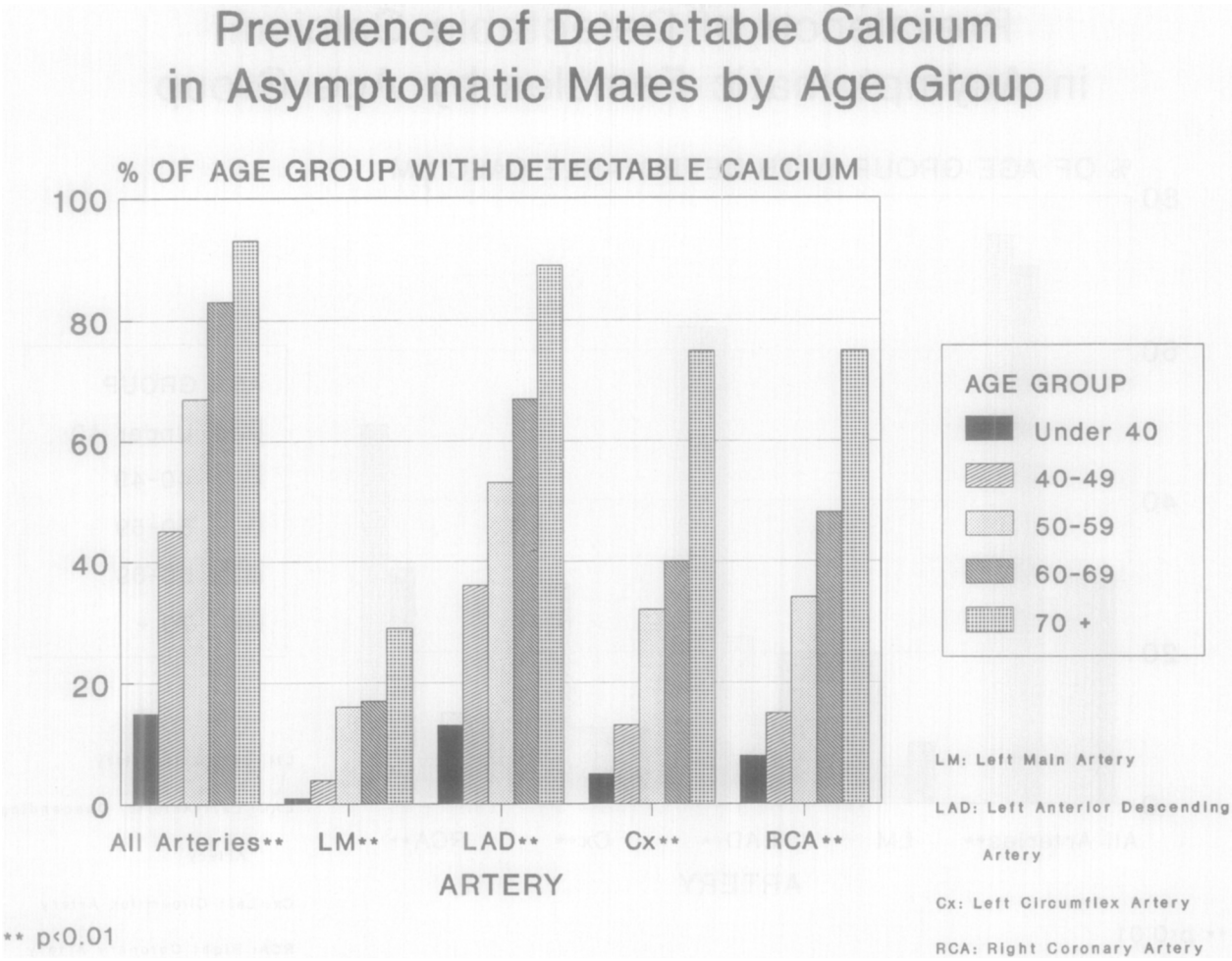

Fig. 3. Prevalence of coronary artery calcium by gender and age group for all patients and by indicated coronary artery in men.

OBSERVATIONS

Six hundred seventy-five men and 190 women aged 22 to 85 (mean ± SD = 51.9 ± 10.1) are included in this report; 79% had at least 1 risk factor and 42% had ≥2 reported principal risk factors among the following: past or current smoking (39%), diabetes (6%), hypercholesterolemia (53%), hypertension (25%), a family history of premature CHD (20%), or obesity (19%).

The mean total calcium score and the prevalence of detectable CAC deposits increased significantly ($p < 0.01$) in all arteries (Table I) and in each major coronary artery by age group in men (Fig. 3) and women with no symptoms (Fig. 4) separately. An increase in the prevalence of detectable CAC deposits is seen at an earlier age in men than in women, as demonstrated by the large increase in prevalence among men between ages 40 to 49 (45%) and 50 to 59 (67%) and in women between the ages of 50 and 59 (27%) and 60 to 69 (71%). In addition, nearly 84%

Table I. Mean (± SD) total calcium score and prevalence of detectable calcium (score >0) in all arteries of patients with no symptoms by age group

	Males		*Females*	
Age (yr)	*Mean ± SD (n)*	*>0*	*Mean ± SD (n)*	*>0*
<40	23.7 ± 86.4 (75)	15%	1.6 ± 4.1 (10)	30%
40-49	34.9 ± 94.8 (240)	45%	7.6 ± 21.2 (50)	30%
50-59	115.7 ± 274.7 (212)	67%	36.5 ± 119.4 (63)	27%
60-69	291.9 ± 504.3 (120)	83%	69.5 ± 130.3 (51)	71%
70+	928.4 ± 1036.1 (28)	93%	137.3 ± 259.6 (16)	75%
Overall	141.8 ± 388.7 (675)	57%	44.4 ± 156.2 (190)	44%
	*$p < 0.0001$	$p < 0.001$	*$p < 0.0001$	$p < 0.001$

*Based on ANOVA done on natural-log transformed data to improve normality of compared distributions.

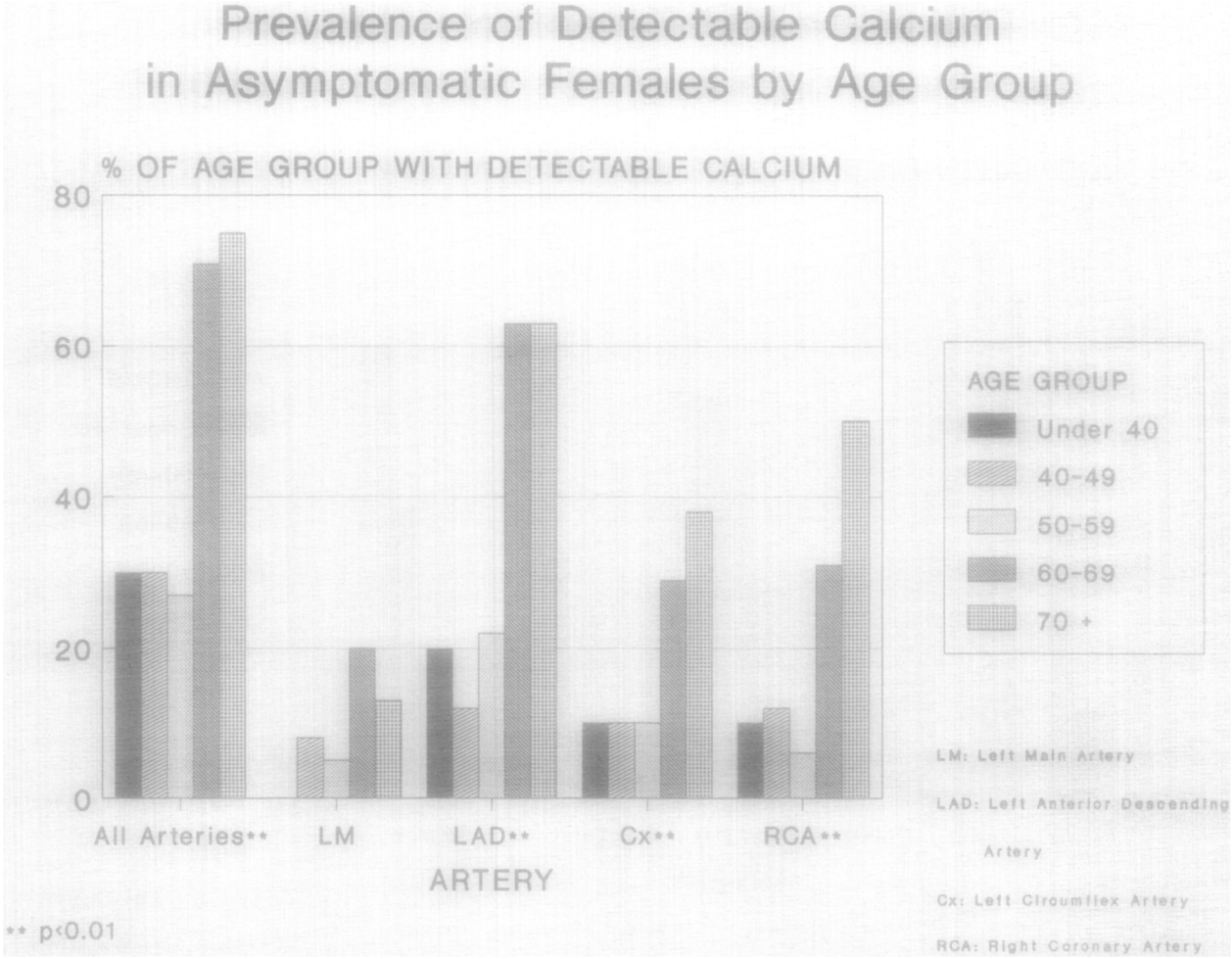

Fig. 4. Prevalence of coronary artery calcium by gender and age group, for all patients and by indicated coronary artery in women.

of subjects under age 40 with no symptoms had no CAC deposits, and only a minority of its subjects (7% of men and 25% of women age ≥70) had no CAC deposits. In both men and women, CAC deposits were most common in the left anterior descending artery.

A significantly ($0.001 < p < 0.05$) higher prevalence of detectable CAC deposits were seen among men with no symptoms with versus without hypertension (72% vs 52%), diabetes (79% vs 56%), hypercholesterolemia (63% vs 51%), previous smoking (63% vs 53%), infrequent exercise (59% vs 48%), and obesity (69% vs 54%). Mean body mass index was also significantly ($p < 0.05$) higher in men with versus without CAC deposits. In women with no symptoms, the prevalence of detectable CAC deposits was significantly greater only among those with versus without a reported history of hypercholesterolemia (50% vs 35%; $p < 0.05$), although CAC deposit prevalence was generally higher in the presence of other risk factors (Table II).

There was a significant ($p < 0.01$) continuous graded relation between the mean total calcium score and prevalence of CAC deposits with the number of risk factors present in men with no symptoms. In men with no risk factors, the prevalence of calcium was 40%, which increased to 74% in those with three or more risk factors. Similar relations were also seen in women with no symptoms. The prevalence of CAC deposits was 29% in women with no risk factors. However, it increased to 64% in those with three or more risk factors (Table IIIA). Additionally, in men the graded relation between prevalence of calcium and risk factors is limited only to those under age 60

Table II. Prevalence of detectable (calcium score >0) and significant calcium in all arteries of patients with no symptoms by self-reported cardiovascular risk factors.

Percentage with risk factor		*Percentage with detectable calcium deposits*	
		Males (n = 675)	*Females (n = 190)*
Hypertension (M 24.3%; F 26.3%)	Yes	72%†	55%‡
	No	52%	40%
	RR	1.39	1.39
Diabetes (M 5.8%; F 8.5%)	Yes	79%†	56%
	No	56%	43%
	RR	1.43	1.32
Hypercholesterolemia (M 51.5%; F 57.8%)	Yes	63%†	50%*
	No	51%	35%
	RR	1.24	1.41
Family history of premature MI (M 18.7%; F 22.9%)	Yes	54%	49%
	No	58%	41%
	RR	0.93	1.18
Previous smoking (M 40.9%; F 32.5%)	Yes	63%*	51%
	No	53%	40%
	RR	1.19	1.27
Infrequent exercise (M 28.9%; F 41.4%)	Yes	59%*	36%
	No	48%	35%
	RR	1.23	1.02
Obesity (M 20.4%; F 15.3%)	Yes	69%*	55%
	No	54%	42%
	RR	1.66	1.59
Body mass index (kg/m^2) by calcium status	Yes	27 ± 4†	26 ± 4
	No	26 ± 3	26 ± 4

*$p < 0.05$, †$p < 0.01$, and ‡$p < 0.10$, compared to those without indicated risk factor (except for body mass index, where comparison is to those without calcification: males, $n = 648$ and women, $n = 184$.)

Table IIIA. Mean (± SD total calcium score and prevalence of detectable calcium (score >0) in all arteries of patients with no symptoms by number of risk factors

	Males		*Females*	
*No. of risk factors	*Mean ± SD (n)*	*>0*	*Mean ± SD (n)*	*>0*
0	79.1 ± 299.9 (119)	40%	35.3 ± 174.4 (35)	29%
1	158.2 ± 441.5 (246)	56%	24.9 ± 32.3 (66)	39%
2	128.0 ± 313.4 (188)	62%	33.3 ± 77.9 (54)	46%
≥3	220.4 ± 494.0 (86)	74%	122.0 ± 320.1 (28)	64%
	$p < 0.0001$	$p < 0.001$	$p = 0.02$	$p = 0.03$

*Reported history of high blood pressure, high blood cholesterol, diabetes, smoking, and family history of premature (before age 55) myocardial infarction.

years; a prevalence of CAC deposits exceeding 80% was seen in older men, regardless of the number of risk factors present. In women the prevalence of calcium tended to be lower in those with fewer risk factors, although it was >50% regardless of the number of risk factors present in those aged 60 and older (Table IIIB).

Stepwise multiple logistic regression (Table IV) showed age (RR = 2.82 per 10 years), female gender (RR = 0.34), history of hypercholesterolemia (RR = 1.63), obesity (RR = 2.22) (all $p < 0.01$), diabetes (RR = 2.32), and a history of hypertension (RR = 1.53; both $p < 0.05$), to be independently predictive of having CAC deposits. Multiple linear regression (Table V) showed similar risk factors to be associated with total CAC deposit score as the logistic regression, except that smoking instead of obesity was a more important indicator of amount as opposed to prevalence of CAC deposits.

COMMENTS

Atherosclerosis as marked by the presence of CAC deposits by ultrafast CT is highly prevalent and is almost a universal finding in older, individuals with no symptoms. The strong positive correlation of age with prevalence of CAC deposits in men and women and the higher prevalence of CAC deposits in men compared to women, supports findings of others.[16] Among our cohort, the prevalence of CAC deposits in men increases in a graded manner until age 60, after which approximately 4 out of 5 men have calcium. In women, however, CAC deposit prevalence is low until after age 60, when there is a dramatic jump to levels similar to that of men. This pattern was also true for CAC deposits in each of the left anterior descending, circumflex, and right coronary arteries. This is consistent with the rapid increase in the risk of coronary events in women after menopause.

The significance of the high prevalence of CAC deposits we report can be clarified by an understanding that CAC deposition occurs only when atherosclerosis is present; however, atherosclerosis can be present without CAC. Therefore atherosclerosis prevalence is likely to be higher than calcium prevalence, and the high prevalence of calcium in elderly persons likely reflects the almost universal presence of atherosclerosis in this age group. Also, CAC deposit prevalence

Table IIIB. Prevalence (%) of coronary calcium by no. of risk factors, gender, and age group

Age group	Males				Females			
	No. of risk factors				No. of risk factors			
	0	1	2 or more	p Value	0	1	2 or more	p Value
<50	18%	34%	51%	<0.001	19%	33%	40%	0.41
(n)	(62)	(109)	(125)		(16)	(27)	(15)	
50-59	50%	64%	77%	0.01	13%	14%	36%	0.13
(n)	(36)	(73)	(94)		(8)	(21)	(33)	
≥60	86%	84%	82%	0.89	55%	78%	74%	0.37
(n)	(21)	(64)	(55)		(11)	(18)	(34)	

Table IV. Indicators of coronary artery calcium: Multiple logistic regression analyses (n = 800)

Risk factor	Coefficient	Risk ratio (odds of calcium)	95% confidence interval
Intercept	−5.50		
Age (10 yr)	1.04	2.82†	(2.33,3.43)
Female gender	−1.07	0.34†	(0.23,0.50)
Hypertension (yes/no)	0.42	1.53*	(1.03,2.25)
Diabetes (yes/no)	0.84	2.32*	(1.06,5.08)
Hypercholesterolemia (yes/no)	0.49	1.63†	(1.18,2.24)
Obesity (yes/no)	0.80	2.22†	(1.47,3.34)

*$p < 0.05$.
†$p < 0.01$.

Table V. Multiple linear regression predicting total calcium score (n = 800)

Risk factor	Coefficient§
Intercept	−1.10
Age (10 yr)	1.09†
Female gender	−1.28†
Hypertension (yes/no)	0.40*
Diabetes (yes/no)	1.03†
Hypercholesterolemia (yes/no)	0.35*
Smoking (yes/no)	0.33*
Obese (yes/no)	0.35‡

*$p < 0.05$.
†$p < 0.01$.
‡$0.05 \leq p < 0.10$.
§Represents natural-log transformed values; regression was computed using natural-log transformed calcium scores as dependent variable.

will always exceed expected coronary event risk, emphasizing the need for more refined criteria to indicate "significant risk." Evaluation of calcified lesion volumes and arterial distribution may aid in providing better prediction along with a known risk factor profile. Moreover, a requirement for stricter criteria to define a "positive" screen should be considered (e.g., a higher cutoff for score or number of calcified pixels). Any utilized score, however, requires extensive validation, such as with in vitro determinations of calcium quantity. Correction for partial volume, lesion location, and other factors potentially affecting observed scores need to be considered.

Although our findings on calcium prevalence are most generalizable to a "high-risk" population with no symptoms, the prevalence of most risk factors reported in our study sample are not markedly different from that expected in a more general population with no symptoms, so the data presented are not necessarily unrepresentative of the general population.

Our risk factor associations with CAC deposits suggest an important role of standard risk factors in promoting subclinical coronary artery disease, further emphasizing the importance of controlling modifiable risk factors detected in individuals with no symptoms. Others have also shown CAC deposits to be associated with total[16] or low-density lipoprotein-cholesterol.[23] An association of previous tobacco use and diabetes with CAC deposits has been demonstrated previously from autopsy reports.[24, 25] Also, a preliminary report by our group on a limited sample showed similar risk factor relations in a mixed group of patients, including those with coronary disease.[26] Other investigations[27, 28] have found selected risk factors to be associated with coronary atherosclerosis, but these studies have been limited to invasive coronary angiography. This generally requires a symptomatic population, by definition, to be referred.

Finally, we note that the total calcium score and prevalence of CAC deposits increases in a graded fashion with the number of risk factors. Lee et al.[23] also reported significantly higher calcium scores among those with three or more risk factors compared with two or fewer, and Bakdash et al.[29]

reported the number of nonlipid coronary risk factors to be related to CAC deposits. We demonstrate, however, that this relation of CAC deposit prevalence and risk factors is nonexistent in men after age 60, where four of five men have CAC deposits regardless of risk factor status. Women under age 60 with fewer than two risk factors are unlikely to have CAC deposits. These data suggest a potentially greater role of CHD risk factors on the development of subclinical atherosclerosis (as marked by CAC deposits) in younger adults, and that CAC deposit screening focusing simply on the prevalence of calcium may have limited use in older adults.

The role of coronary screening by ultrafast CT has recently received attention because of its potential to discriminate, noninvasively, people who may have coronary atherosclerosis. Recent studies in symptomatic patients with ultrafast CT have shown a strong relation between coronary calcium and angiographic coronary artery disease,[21, 30, 31] including the number of diseased vessels. High sensitivity is noted for obstructive disease, where all or nearly all such patients have CAC deposits, but reduced sensitivity is seen in those with nonobstructive disease[31-32] (e.g., angiographic obstruction of >50%, a likely scenario in many patients with no symptoms, but where coronary events also can occur). Also, although the absence of coronary calcium is highly specific to rule out obstructive angiographic disease,[33] this does not mean mild disease is not present[32] in those without CAC deposits.

Longitudinal investigation is needed to determine whether calcific deposits defined by ultrafast CT coronary artery scanning (and progression of calcium seen from serial studies) in combination with known risk factors can better enable physicians to evaluate subsequent risk of coronary events. Long-term follow-up data on clinical event risk in relation to calcium score and other CAC deposit indexes such as lesion volume and arterial distribution are needed. Such studies may also provide the needed data to evaluate the cost-effectiveness of coronary scanning (about $375) compared to other noninvasive assessment for coronary disease. Our data show a high prevalence of atherosclerosis in adults with no symptoms that dramatically rises with age to become nearly universal in the elderly. Coronary risk factors are also implicated in the development of subclinical, calcified atherosclerosis in middle-aged persons with no symptoms. Persons with established risk factors and CAC deposits may be indicated, in particular, for aggressive risk factor intervention, as has been suggested for persons who have been documented as having CHD by other tests. Nevertheless, the absence of CAC deposits does not diminish the importance of controlling any risk factors that may be present.

SUMMARY

We evaluated 675 men and 190 women who had no symptoms or history of clinical CHD, to determine the prevalence and risk factor correlates of CAC deposits as a marker of atherosclerosis. Measurements were taken noninvasively by ultrafast CT. The presence and extent of CAC deposits as measured by ultrafast CT was determined in all subjects, who also received personal and family medical history and risk factor questionnaire. The prevalence of CAC deposits increased significantly with age, ranging from 15% and 30% in men and women, respectively, <40 years of age to 93% and 75% in those aged ≥70 years. Prevalence and total score also increased by the number of risk factors present, although in those aged >60 years a high prevalence (>80% in men) of calcium was present regardless of the presence of risk factors. In multiple logistic regression, age, male gender, hypertension, diabetes, hypercholesterolemia, and obesity were independently associated with CAC deposits. These results suggest a high prevalence of atherosclerosis with increasing age and the presence of risk factors in men and women who have no symptoms. Studies to determine the prognostic value of CAC in individuals with no symptoms are needed to determine which populations may benefit most from CAC deposit screening.

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Dual-balloon progressive coronary dilatation catheter: Design and initial clinical experience

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